REMARKS

Amended Claims

Applicants have cancelled Claims 2, 4-6, 8, 10-12, 14,16-18, 20, and 22-24. Claims 1, 3, 7, 9, 13, 15, 19 and 21 have been amended. Claims 25-45 have been added. Claims 25, 26, 29, 30, 33, 34, 37, and 38 specify the number of CDRs modified in the population of nucleic acids encoding heavy chain or light chain variable regions. Claims 27, 28, 31, 32, 35, 36, 39, and 40 are directed towards coexpressing the population of nucleic acids constructed with nucleic acids encoding either a heavy chain or light chain variable region so as to produce a diverse population of altered heteromeric variable regions comprising a light and a heavy chain. Claims 41-45 are directed to a method of constructing a population of antibody variable regions. Basis for amendments and new claims can be found throughout the Specification, including on page 7, lines 22-25 and page 31, lines 5-11. As such, Applicants submit no new matter has been added.

The Invention

The present invention is drawn to constructing libraries of heavy and/or light chain variable regions in which non-human CDRs that have been altered are grafted onto unmodified human acceptor frameworks and modifying only the non-human CDRs to reacquire or maintain binding affinity or to improve binding affinity to a target antigen. The claimed invention is distinguished from prior humanization approaches in that the antibodies are compromised of a human framework be that has not been modified. Binding affinity is maintained or reacquired or improved solely through the modification of the donor CDRs. In light of these comments and the arguments below, Applicants submit the pending claims are patentable and respectfully request allowance.

REJECTIONS

Claims 1-2, 6-10, 12-16, 18-22 and 24 stand rejected under 35 U.S.C. 103(a) as unpatentable over Jones et al.. (Nature 321:522, 1986), Yelton et al. (The Journal of Immunology 155:1994-2004, 1995), Soderlind et al. (Gene 160:269-272, 1995) and Hagiwara et al. (U.S. Patent 5,589,573, issued 12/96).

Claims 1-2, 6-10, 12-16, 18-22 and 24 stand rejected under 35 U.S.C. 103(a) as unpatentable over Jones et al. (Nature 321:522, 1986), Wu et al. (PNAS 95:6037-6042, 5/98) and Soderlind et al. (Gene 160:269-72, 1995) and Hagiwara et al. (U.S. Patent 5,589,573, issued 12/96).

I. **The rejection under 35 U.S.C. 103 over Jones, Yelton, Soderlind and Hagiwara**

Claims 1-2, 6-10, 12-16, 18-22 and 24 stand rejected under 35 U.S.C. 103(a) as unpatentable over Jones et al., Yelton et al., Soderlind et al. and Hagiwara et al..

Applicants submit the Examiner has not established a prima facie case of obviousness as there is no motivation to combine the references cited by the Examiner, and because one of the references actually suggests that the method claimed by Applicants is not likely to work. Further, even if a prima facie case were established, there is no suggestion in the art to mutate one or more CDRs in the context of an unmodified acceptor framework to reacquire or improve binding affinity with respect to a donor sequence. The art at the time taught that the preferable route to humanization involved modifying human framework regions in the context of a murine CDR. There was no suggestion to work with unmodified human frameworks and preserve or improve binding affinity solely through mutation of multiple CDRs.

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of

> ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claims limitations. MPEP 706.02(j).

A. There is no motivation to combine the teachings of Jones et al. and Yelton et al.

In the Rejection mailed 13-Mar-2003, the Examiner alleges asserted that Jones et al. teaches grafting of mouse CDRs onto human acceptor frameworks resulting in a loss of affinity when compared to the parent antibody. Yelton et al. was cited for teaching affinity maturation of an antibody by mutagenesis of the CDRs and constructing random libraries in the heavy chain. Further, Yelton et al. stated that the light chain would also be examined. Soderlind et al. was cited for teaching libraries of variable domains in which the CDRs were modified and the framework was left unchanged and the libraries were made with overlapping oligonucleotides. The Examiner also alleges that Hagiwara et al. taught amino acid sequence from a database and that the sequences could be retrieved by a computer. The Examiner alleges suggested that one of ordinary skill in the art would have been motivated to and would have a reasonable expectation of success because

> Jones et al. teach[es] CDR grafting onto a human framework and the antibody has a lower affinity than the murine antibody and it would be obvious to use the mutagenesis strategy of Yelton et al. to produce a library of CDR mutants and keep the framework residues constant because Yelton et al. teach antibodies which resulted in improved affinity only by altering the CDRs. (Rejection mailed 13-Oct-2003)

Applicants respectfully disagree with the Examiner that one of skill in the art would have been motivated to combine the teachings of Jones et al., Yelton et al., Soderlind et al. , and Hagiwara et al. to arrive at the Applicants' invention.

Specifically, Applicants submit that one of skill in the art would not be motivated to combine the teachings of Jones et al. and Yelton et al. because the general state of the art taught away from using the teachings of Yelton et al. when grafting mouse CDRs onto a human acceptor framework. The Examiner alleges that one of skill in the art would look to Yelton et al. to improve the affinity of the antibody of Jones. Applicants submit that Yelton

et al. teaches affinity maturation by modifying the CDRs in the context of an antibody which comprises its original CDRs. In Yelton et al., the CDRs were not grafted onto an acceptor framework. The CDRs of a mouse monoclonal Fab were modified while the mouse framework was left unchanged. As the CDRs were already in their original framework, there was no need to modify the framework. This is a key distinction from the present invention in which mouse CDRs are grafted into an unmodified human framework and the CDRs are modified to maintain, improve or reacquire affinity. The general humanization approach to minimize potential immunogenicity concerns involved transferring mouse CDRs into human acceptor frameworks and then modifying the human acceptor frameworks to maintain binding affinity. Since the mouse CDRs were responsible for antigen specificity, the goal was to preserve those CDRs in the context of a mutated human framework. There was no motivation to modify the CDRs once they had been grafted into a different framework. Yelton et al. focused on modifying CDRs because those CDRs had not been grafted into a new framework. Thus, there was no motivation to introduce an additional variable associated with mutated CDRs in the context of a different framework. As demonstrated in several references (Queen et al., Reichmann et al. and Co et al.), when grafting mouse CDRs onto a human framework, one of skill in the art looked to modifying the framework and not modifying the CDRs to try to improve affinity. Applicants respectfully submit that there is no motivation to combine the teachings of Jones et al. and Yelton et al. in view of Soderlind and Hagiwara to arrive at the present invention.

In the rejection mailed June 8, 2004 (Paper No. 20040415), the Examiner also used Yelton et al. as "providing motivation to use affinity maturation of antibodies." The Examiner stated, "Yelton clearly acknowledges advances in altering the structure of antibodies to improve the therapeutic potential. . . . [T]aken in its whole, Yelton teach there is a clear advantage to have higher affinity antibodies and using these antibodies for therapy which can be humanized (see page 4 of Paper No. 20040415)." Contrary to the Examiner's assertion, Yelton et al. does not teach there is a clear advantage to affinity mature an antibody to improve therapeutic potential.

Specifically, page 2002 of Yelton states

> [t]he range of Ab affinities best suited for optimizing the potency and efficacy of Ab-targeted therapeutic agents is controversial. Mathematical and computer models designed to examine how various factors influence Ab

> distribution in a tumor have suggested that increasing the affinity of an Ab may not bring a therapeutic advantage . . . . Few studies have examined the issue empirically, and the results are conflicting.

Therefore, Yelton actually teaches there may be no clear advantage of affinity maturing an antibody by altering the structure of a portion of the antibody-binding region.

Since Yelton does not provide the motivation or suggestion to combine the references, Applicants submit that the Examiner has not established a prima facie case of obviousness.

B. The art as a whole teaches away from combining the Yelton et al. and Jones et al.

The present invention is not obvious as the art as a whole taught away from the claimed invention at the time of filing. The Examiner asserts that one of skill in the art would look to Yelton et al. to improve the affinity of the antibody made according to Jones et al. (i.e. when unmodified mouse CDRs were grafted onto an unmodified human acceptor framework). Applicants respectfully submit the art taught it would be necessary to modify the human acceptor framework in order to retain affinity to the target antigen when grafting mouse CDRs onto the human acceptor framework. For example, Reichmann et al. teaches that grafting mouse CDRs onto a human acceptor framework results in an antibody that binds poorly to its target antigen. To address this problem, the authors modified framework residues, not the mouse CDRs. Specifically, the authors stated "alterations in the 'Kabat' framework region can enhance the affinity of the antibody . . . ." (Reichmann et al. page 326). Further, Queen et al. also teaches that framework residues must be modified when grafting mouse CDRs onto a human framework. In Queen et al., mouse CDRs were grafted onto human frameworks that had been modified by incorporating mouse residues at certain framework positions to try to reduce immunogenicity but also "to better preserve the precise structure of the CDRs . . . ." (Queen et al. page 10031). Finally, Co et al., also teaches that it is desirable to modify framework residues to try to minimize distortions in the grafted mouse CDRs. Specifically, Co states

> "However, generation of other fully humanized antibodies has proved unexpectedly difficult, because significant loss of binding affinity generally resulted from simple grafting of hypervariable regions, probably due to

distortion of the complementarity-determining region (CDR) conformation by the human framework." (Co et al., Page 2869)

Therefore, Applicants submit that the present claimed invention drawn to constructing libraries of heavy and light chain variable regions in which non-human CDRs are grafted onto human acceptor frameworks coupled with modifying only those non-human CDRs would not have been obvious because the art taught away from modifying only the donor CDRs when grafted into a human acceptor framework.

II. The rejection under 35 U.S.C. 103 over Jones et al., Wu et al., Soderlind et al. and Hagiwara et al.

A. There is not motivation to combine the teachings of Jones et al. and Wu et al.

Applicants submit that this combination of references also does not establish a prima facie case of obviousness as there is no motivation to combine this cited art.

The Examiner asserts the pending claims are obvious in view of Jones et al., Wu et al., Soderlind et al. and Hagiwara et al. because Jones et al. teaches CDR grafting of non-human CDRs into a human framework resulting in an antibody with lower affinity than the non-human donor antibody. The Examiner suggests that "it would be obvious to use the mutagenesis strategy of Wu et al. to produce a library of CDR mutants and keep the framework residues constant because Wu et al. teach antibodies which resulted in improved affinity only by altering the CDRs." (p. 6 Paper No. 20040415). Applicants respectfully disagree that a person of skill in the art would be motivated by the Jones et al., Wu et al., Soderlind et al., and Hagiwara et al. references to construct libraries in which the non-human donor CDRs were modified and grafted into an unmodified human acceptor framework.

As the Examiner admits, Jones teaches that grafting a mouse CDR into a human acceptor framework results in a lower binding affinity than the parent mouse donor antibody. The art, however, teaches that to remedy this binding affinity loss, one would modify the human framework residues. The state of the art as evidenced by Reichman et al. (Nature 332, 323-327) and Queen et al. (PNAS 86, 10029-10033, 1989) was to modifying the human acceptor framework after grafting donor mouse CDRs into such a framework. The methodology provided by Jones et al., Reichmann et al. and Queen et al. teaches that grafting

of mouse CDRs onto a human framework results in loss of affinity when compared to the donor mouse antibody. To improve affinity, Reichmann et al. and Queen et al. teach modifying the human framework and not the mouse CDRs. As suggested by Queen et al., one of skill in the art would look to modifying the human acceptor frameworks and not modifying the mouse CDRs when grafting onto an unmodified human acceptor framework.

For the foregoing reasons, Applicants submit that a prima facie case of obviousness has not been made and respectfully request that the rejection be withdrawn.

III. The rejection under 35 U.S.C. 103(a) and the Soderlind reference.

Applicants submit that there is no motivation to combine the teachings of Soderlind et al. with the cited art used in the present rejections under 35 U.S.C. 103(a). Soderlind et al. teaches modifying CDRs in the context of an original framework and not, as in the present invention, where mouse CDRs are grafted onto an unmodified human framework. Because Soderlind does not involve CDR grafting, it provides nothing more than a mutagenesis study involving a known protein which may or may not affect that protein's properties. As stated above, one of ordinary skill in the art would not look to modifying only the CDRs when grafting mouse CDRs onto a human acceptor framework. Therefore, as Soderlind teaches modifying the CDRs in the context of an original framework, there would be no motivation to combine Soderlind with the teachings of Wu et al. and Jones et al. or Yelton et al. and Jones et al.

Therefore, Applicants submit that there is no motivation to combine the teachings of Soderlind with those of Jones et al. and Yelton et al. or with the teachings of Jones et al. and Wu et al. and as such a prima facie case of obviousness has not been made. For the foregoing reasons, Applicants respectfully request the withdrawal of the rejection of the claims.

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CONCLUSION

Applicants submit that a prima facie case of obviousness has not been made because there is no motivation to combine the teachings of Jones et al., Yelton et al., Soderlind et al. and Hagiwara et al. In addition, there is no motivation or suggestion to combine the teachings of Jones et al., Wu et al., Soderlind et al., and Hagiwara et al. Applicants also submit that even if a case of prima facie obviousness has been made (which Applicants do not admit), the present invention is not obvious because the art as a whole teaches away. Applicants respectfully request that the pending rejections be withdrawn and the present claims be allowed. If, for any reason, the Examiner feels that a telephone conversation would be helpful in expediting the prosecution of this case, the Examiner is urged to call me.

Respectfully submitted,

Mark J. Stewart
Attorney for Applicants
Registration No. 43,936
Phone: 317-276-0280

Eli Lilly and Company
Patent Division/MJS
Lilly Corporate Center
Indianapolis, Indiana 46285

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